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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,818	01/20/2004	Edward A. Dratz	MONT-058/02US 306509-2189	4463
58249 7590 06/12/2008 COOLEY GODWARD KRONISH LLP ATTN: Patent Group Suite 1100 777 - 6th Street, NW WASHINGTON, DC 20001			EXAMINER RAMILLANO, LORE JANET	
			ART UNIT 1797	PAPER NUMBER
			MAIL DATE 06/12/2008	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/761,818	<b>Applicant(s)</b> DRATZ ET AL.	
	<b>Examiner</b> LORE RAMILLANO	<b>Art Unit</b> 1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 02 April 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 58-83 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 77 and 78 is/are allowed.
- 6) ☒ Claim(s) 58-76 and 79-83 is/are rejected.
- 7) ☒ Claim(s) 58,62,63,65,68,69,75,79 and 82 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 January 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of Claims***

1. In applicant's reply filed on 4/2/08, applicant cancelled claims 1-16 and added new claims 58-83.

### ***Response to Amendment***

#### ***Claim Objections***

2. Claims 58, 62, 63, 65, 68, 69, 75, 79, and 82 are objected to because of the following informalities:

Claims 58, 62, 63, 69, 75 are objected to because "quarternary" is misspelled. For examination purposes, examiner will interpret quarternary to be quaternary.

Claim 65 is objected to because it does not appear that it properly depends on claim 61 since claim 61 and claim 58 do not recite the limitation, "photocleavable moiety." For examination purposes, examiner will interpret claim 65 to depend on claim 64.

Claim 68 is objected to because it does not appear that it properly depends on claim 66 since claim 66 and claim 58 do not recite the limitation, "sulfhydryl-reactive linker." For examination purposes, examiner will interpret claim 68 to depend on claim 67.

Claims 79 and 82 are objected to because it is not clear whether applicant intended these claims to be dependent on claim 58 or to be independent claims. For examination purposes, examiner will interpret these claims to be dependent on claim 58.

Appropriate corrections are required.

***Claim Rejections - 35 USC § 112***

3. The rejection of claim 10, under 35 U.S.C. 112, second paragraph, is withdrawn.

In light of applicant's amendments, a new rejection follows.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 58-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 58 is objected to because it cannot be determined which group, in the claim language, "the pk of the group," applicant is referring to in subpart (c) of this claim.

***Prior art rejections***

6. In light of applicant's cancellation of the prior claims and the additional subject matter added to the new claims, the rejections over the prior art are withdrawn. New rejections follow.

***Claim Rejections - 35 USC § 103***

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. **Claims 58-76 and 79-83** are rejected under 35 U.S.C. 103(a) as being unpatentable over Haugland et al. ("Haugland," US 6972326) in view of in view of Masters (US 5362422).

Haugland discloses an optical labeling molecule comprising a zwitterionic dye moiety, a titrable group moiety, and a functional linker moiety (i.e. column 4, line 3 to column 7, line 27). Haugland further discloses a cleavable moiety, isotope labels, amine-reactive linkers, thiol-reactive linkers, other linkers, and various structural formulas (i.e. column 9, lines 55 to column 10, lines 36). In particular Haugland discloses the labeling molecule having the general structure: T-ZD-A in claim 18, column 39; and ZD-T-A in claim 16, column 38.

While Haugland does not specifically disclose having the general structure: T-ZD-C-A; T-ZD-C-I-A; and ZD-T-C-I-A, Haugland discloses alternative dipyrrometheneboron difluoride dyes, which are commercially available under the trademark BODIPY dyes (see Table 1). In addition, because Haugland discloses that the dipyrrometheneboron difluoride dyes are applied in various research projects, which include proteomic research, the dipyrrometheneboron difluoride dyes are capable of having different structural configurations to make them compatible with the component to be detected or analyzed. (i.e. column 18, lines 9-21). Thus, it would have been obvious to a person of ordinary skill in the art to modify Haugland's optical labeling molecule to have a general structure: T-ZD-C-A; T-ZD-C-I-A; and ZD-T-C-I-A, because it would be desirable to have a labeling dye which is capable of labeling any particular component to be detected or analyzed.

As to claim 58, Haugland does not specifically disclose having a quaternary ammonium group or a sulfonate group that is not titratable between the pH of 3-12. Masters discloses that zwitterionic compounds preferably contain a quaternary

ammonium group and a sulfonate group because such groups maintain their zwitterionic character over most of the pH range. It would have been obvious to a person of ordinary skill in the art to modify Haughland's cationic and anionic groups to be non-titratable between the pH of 3-12 because it would be desirable to utilize cationic and anionic groups that maintain their amphoteric character over a wide pH range (i.e. Masters, col. 2, lines 23-36).

9. **Claims 58-61, 64, 67, 68, 70-72, 79-83** are rejected under 35 U.S.C. 103(a) as being unpatentable over Meltola et al. ("Meltola," US 7198958) in view of Masters.

As to claims 58, 67, 68, in Fig. 2c (i.e. Compound 8), Meltola discloses an optical labeling molecule for labeling a target analyte comprising (a) a zwitterionic dye moiety comprising at least one positive or at least one negative charge moiety added to obtain a net neutral charge, wherein the positive charge moiety is selected from a group consisting of a quaternary ammonium group, and a positive charge group (i.e. col. 7, lines 38-46), or a negative charge moiety that is selected from the group consisting of a sulfonate group (i.e. compound 8); (b) a functional linker moiety (i.e. Compound 8, aldehyde, sulfonylchloride-reactive linker, and sulfhydryl-reactive linker consisting of maleimide, col. 8, lines 39-46); and a titratable group moiety (i.e. tertiary amine in Fig. 7, compound 43).

As to claim 58, Meltola does not specifically disclose having a quaternary ammonium group or a sulfonate group that is not titratable between the pH of 3-12. Masters discloses that zwitterionic compounds preferably contain a quaternary ammonium group and a sulfonate group because such groups maintain their

zwitterionic character over most of the pH range. It would have been obvious to a person of ordinary skill in the art to modify Meltola's cationic and anionic groups to be non-titratable between the pH of 3-12 because it would be desirable to utilize cationic and anionic groups that maintain their amphoteric character over a wide pH range (i.e. Masters, col. 2, lines 23-36).

As to claim 59, Meltola discloses the zwitterionic dye moiety comprises a chromophore responsible for a detectable optical signal (i.e. 2, lines 21-38).

As to claim 60, Meltola reads on the claim language recited in claim 60 because the claim recites a process claim, which is of no patentable moment as to a compound type of claim.

As to claim 61, Meltola discloses that the titratable group moiety is a tertiary amine (i.e. fig. 2c, Compound 8).

As to claim 64, Meltola discloses a cleavable moiety selected from a group consisting of a chemical moiety and an enzymatically cleavable moiety (i.e. col. 8, lines 31-39).

As to claim 70, Meltola discloses the labeling molecule having the general structure: T-ZD-A- wherein ZD is the zwitterionic dye moiety, T is the titratable moiety, and A is the linker moiety (i.e. fig. 2c, Compound 8).

As to claim 71, Meltola discloses the labeling molecule having the general structure: ZD-T-A- wherein ZD is the zwitterionic dye moiety, T is the titratable moiety, and A is the linker moiety (i.e. fig. 2e, compound 14).

As to claim 72, Meltola discloses the labeling molecule having the general structure: T-ZD-C-A- and ZD-T-C-A wherein ZD is the zwitterionic dye moiety, T is the titratable moiety, C is the cleavable moiety, and A is the linker moiety (i.e. fig. 2b, compound 6).

As to claims 79-81, Meltola discloses a cellular component selected from the group consisting of proteins, carbohydrates, nucleic acids covalently attached to the optical labeling molecule of claim 58 (i.e. col.7, lines 38-40, col. 18, lines 55-60).

As to claims 82-83, Meltola reads on the steps of preparing the optical labeling molecule because it teaches the end product of this process, as cited above. Furthermore, Meltola discloses that the zwitterionic dye moiety is a fluorescent dye. (i.e. abstract).

10. **Claims 66, 73, and 74** are rejected under 35 U.S.C. 103(a) as being unpatentable over Meltola in view of Masters, as applied to claims 58-61, 64, 67, 68, 70-72, 79-83 above, and further in view of Loehrlein et al. ("Loehrlein," US Pub. No. 2002/0160361).

The disclosure of Meltola in view of Masters is indicated above. Meltola in view of Masters does not specifically disclose having a second label, wherein the second label comprises a light stable isotope or heavy stable isotope.

Loehrlein discloses that isotopic variants of specified atoms, such as radioisotopes or stable, higher mass isotopes, are used to vary the mass of the amplification product. The radioisotopes can be detected based on the energy released when they decay, and numerous applications of their use are generally known in the art.



Loehrlein further discloses that stable (non-decaying) heavy isotopes can be detected based on the resulting shift in mass, and are useful for distinguishing between two amplification products that would otherwise have similar or equal masses. (i.e. [0172]).

It would have been obvious to a person of ordinary skill in the art to modify the modified optical labeling molecule of Meltola by including a heavy stable isotope because it would be beneficial to include a widely known detection means for detecting the molecule when it is needed to distinguish between two amplification products that would otherwise have similar or equal masses (i.e. Loehrlein, [0172]).

11. **Claims 58-60, 62-64, 67-69, 75, 79-80, and 82-83** are rejected under 35 U.S.C. 103(a) as being unpatentable over Benson et al. ("Benson," US 5936087) in view of Masters.

As to claims 58, 67, 68, in Fig. 7 (i.e. Compound 43), Benson discloses an optical labeling molecule for labeling a target analyte comprising (a) a zwitterionic dye moiety comprising at least one positive or at least one negative charge moiety added to obtain a net neutral charge, wherein the positive charge moiety is selected from a group consisting of a quaternary ammonium group, and a positive charge group (i.e. col. 8, line 49 to col. 10, line 12), or a negative charge moiety that is selected from the group consisting of a sulfonate group and a sulfate group (i.e. i.e. col. 8, line 49 to col. 10, line 12); (b) a functional linker moiety (i.e. N-hydroxysuccinimidyl (NHS) ester, isothiocyanate, aldehyde, sulfonylchloride-reactive linker, sulfhydryl-reactive linker consisting of maleimide and iodoacetamide, col. 4, lines 37-65, col. 8, line 49 to col. 10, line 12); and a titratable group moiety (i.e. amine, col. 8, line 49 to col. 10, line 12).

As to claim 58, Benson does not specifically disclose having a quaternary ammonium group or a sulfonate group that is not titratable between the pH of 3-12. Masters discloses that zwitterionic compounds preferably contain a quaternary ammonium group and a sulfonate group because such groups maintain their zwitterionic character over most of the pH range. It would have been obvious to a person of ordinary skill in the art to modify Benson's cationic and anionic groups to be non-titratable between the pH of 3-12 because it would be desirable to utilize cationic and anionic groups that maintain their amphoteric character over a wide pH range (i.e. Masters, col. 2, lines 23-36).

As to claim 59, Benson discloses the zwitterionic dye moiety comprises a chromophore responsible for a detectable optical signal (i.e. col. 10, lines 59-67, rhodamine is well known in the art to be a chromophore).

As to claim 60, Benson reads on the claim language recited in claim 60 because the claim recites a process claim, which is of no patentable moment as to a compound type of claim.

As to claims 62-63, Benson discloses that the zwitterionic dye moiety comprises at least two quaternary ammonium groups and at least one sulfonate group (i.e. col. 8, line 49 to col. 10, line 12).

As to claim 64, Benson discloses a cleavable moiety selected from a group consisting of a chemical moiety and an enzymatically cleavable moiety (i.e. col. 12, lines 15-68).

As to claim 69, Benson discloses a dye moiety comprising BODIPY, which further comprises at least one added negative charge moiety selected from a sulfonate group and at least one added positive charge moiety selected from a group consisting of a positive charge group (i.e. col. 13, lines 58-63; fig. 7, compound 43).

As to claim 75, Benson discloses (a) a difluoride diaza-indacene-propionic acid (BODIPY) dye moiety, having at least one quaternary ammonium group and at least one sulfonate group; (b) a titratable group moiety wherein the said titratable group is a tertiary amine; and (c) a functional linker moiety wherein such linker is a N-hydroxysuccinimidyl ester (i.e. col. 8, line 50 to col. 10, line 12; col. 11, lines 62-67).

As to claims 79-80, Benson discloses a cellular component selected from the group consisting of proteins, lipids, and nucleic acids covalently attached to the optical labeling molecule of claim 58 (i.e. col. 12, lines 5-14).

As to claims 82-83, Benson reads on the steps of preparing the optical labeling molecule because it teaches the end product of this process, as cited above. Furthermore, Meltola discloses that the zwitterionic dye moiety is a fluorescent dye. (i.e. col. 1, lines 4-6).

**12. Claim 65 and 76** are rejected under 35 U.S.C. 103(a) as being unpatentable over Benson in view of Masters, as applied to claims 58-60, 62-64, 67-69, 75, 79-80, and 82-83 above, and further in view of Meade et al. ("Meade," US 6713045).

The disclosure of Benson in view of Masters is indicated above. Benson in view of Masters does not specifically disclose having a photocleavable moiety that is selected from a group consisting of a O-nitrobenzylic or benzoin moiety.

Meade discloses utilizing, in one embodiment, a blocking moiety that is a photocleavable moiety. That is, upon exposure to a certain wavelength of light, the blocking moiety is cleaved, allowing an increase in the exchange rate of water in at least one coordination site of the complex. This embodiment has particular use in developmental biology fields (cell lineage, neuronal development, etc.), where the ability to follow the fates of particular cells is desirable. Suitable photocleavable moieties are similar to "caged" reagents which are cleaved upon exposure to light. A particularly preferred class of photocleavable moieties are the O-nitrobenzylic compounds, which can be synthetically incorporated into a blocking moiety via an ether, thioether, ester (including phosphate esters), amine or similar linkage to a heteroatom (particularly oxygen, nitrogen or sulfur). Also of use are benzoin-based photocleavable moieties. (i.e. col. 18, lines 16-33). It would have been obvious to a person of ordinary skill in the art to modify the modified optical labeling molecule of Benson by incorporating a benzoin or O-nitrobenzylic compound because both types of compounds are well known in the art as suitable photocleavable moieties for uses in developmental biological fields, where the ability to follow the fates of particular cells is desirable.

13. **Claims 66, 73, and 74** are rejected under 35 U.S.C. 103(a) as being unpatentable over Benson in view of Masters, as applied to claims 58-60, 62-64, 67-69, 75, 79-80, and 82-83 above, and further in view of Loehrlein et al. ("Loehrlein," US Pub. No. 2002/0160361).

The disclosure of Benson in view of Masters is indicated above. Benson in view of Masters does not specifically disclose having a second label, wherein the second label comprises a light stable isotope or heavy stable isotope.

Loehrlein discloses that isotopic variants of specified atoms, such as radioisotopes or stable, higher mass isotopes, are used to vary the mass of the amplification product. The radioisotopes can be detected based on the energy released when they decay, and numerous applications of their use are generally known in the art. Loehrlein further discloses that stable (non-decaying) heavy isotopes can be detected based on the resulting shift in mass, and are useful for distinguishing between two amplification products that would otherwise have similar or equal masses. (i.e. [0172]).

It would have been obvious to a person of ordinary skill in the art to modify the modified optical labeling molecule of Benson by including a heavy stable isotope because it would be beneficial to include a widely known detection means for detecting the molecule when it is needed to distinguish between two amplification products that would otherwise have similar or equal masses (i.e. Loehrlein, [0172]).

14. **Claim 76** is rejected under 35 U.S.C. 103(a) as being unpatentable over Benson in view of Masters, as applied to claims 58-60, 62-64, 67-69, 75, 79-80, and 82-83 above, and further in view of Loehrlein, as applied to claims 66, 73, and 74 above, and further in view of Meade.

The disclosure of Benson in view of Masters, and further in view of Loehrlein, is indicated above. The modified Benson does not specifically disclose having a

photocleavable moiety that is selected from a group consisting of a O-nitrobenzylic or benzoin moiety.

Meade discloses utilizing, in one embodiment, a blocking moiety that is a photocleavable moiety. That is, upon exposure to a certain wavelength of light, the blocking moiety is cleaved, allowing an increase in the exchange rate of water in at least one coordination site of the complex. This embodiment has particular use in developmental biology fields (cell lineage, neuronal development, etc.), where the ability to follow the fates of particular cells is desirable. Suitable photocleavable moieties are similar to "caged" reagents which are cleaved upon exposure to light. A particularly preferred class of photocleavable moieties are the O-nitrobenzylic compounds, which can be synthetically incorporated into a blocking moiety via an ether, thioether, ester (including phosphate esters), amine or similar linkage to a heteroatom (particularly oxygen, nitrogen or sulfur). Also of use are benzoin-based photocleavable moieties. (i.e. col. 18, lines 16-33). It would have been obvious to a person of ordinary skill in the art to modify the modified optical labeling molecule of Benson by incorporating a benzoin or O-nitrobenzylic compound because both types of compounds are well known in the art as suitable photocleavable moieties for uses in developmental biological fields, where the ability to follow the fates of particular cells is desirable.

***Allowable Subject Matter***

15. Claims 77-78 are allowed.

The following is a statement of reasons for the indication of allowable subject matter: the prior art of record Haughland fails to teach or fairly suggest the compound

having formula (I) in claim 77, and the formulas recited in claim 78, in combination with the remaining features and elements of the claimed invention.

***Response to Arguments***

16. Applicant's arguments with respect to claim 1-16 have been considered but are moot in view of the new ground(s) of rejection.

***Conclusion***

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LORE RAMILLANO whose telephone number is (571) 272-7420. The examiner can normally be reached on Mon. to Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-7420.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jill Warden/  
Supervisory Patent Examiner, Art Unit 1797

Lore Ramillano  
Examiner  
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